RANDOMIZATION IN CLINICAL TRIALS

ACF Hui FHKAM (Med)
Senior Medical Officer
Department of Medicine & Therapeutics,
Prince of Wales Hospital

J HK Geriatr Soc 2004; 12:36
Correspondence: ACF Hui
Email: acfhui@cuhk.edu.hk

Clinical trials aim to draw conclusions about the effectiveness of an intervention treatment. Differences in outcomes of interest may be due to the effect of therapy under investigation; imbalances between the control and treatment group; and chance. An investigator may subconsciously allocate patients based on preconceived ideas about the treatment under evaluation. The purpose of random allocation is to attempt to eliminate systematic bias so that the treatment and control groups are similar. In rigorously conducted randomised trials, neither the investigators nor the patients should know beforehand which intervention would be assigned. One investigator, independent of the clinicians, should arrange the sequence of random treatment assignment in advance and be responsible for patient registration and randomisation.

Most trials allocate equal numbers of patients to the treatment and control groups, giving a randomisation ratio of 1:1. Sometimes when the experimental arm employs an expensive drug/ procedure, the process of unequal randomisation could lower costs; it may be more economically efficient to recruit fewer participants to the expensive intervention group. In a trial in which the ratio is 2:1, for every two patients using a cheaper control drug one patient is allocated to the more expensive therapy. This would lead to a modest reduction in statistical power but would produce substantial cost savings.

One example, from acute stroke therapy, of the importance of randomisation is the uncertainly created when published trials are found wanting in this aspect. Recombinant tissue plasminogen activator is the first drug treatment that had been demonstrated in a clinical trial to be of benefit in acute ischaemic stroke [1]. This multicentre trial was conducted by the National Institute of Neurological Disorders and Stroke Study Group and the results showed that rt-PA given within three hours of stroke onset improved clinical outcome in terms of mortality and morbidity, as measured on a number of assessment scales. The baseline clinical severity score was the National Institutes of Health Stroke Scale, an important prognostic variable which grades patients from 0 (no disability) to 51 (maximum). Randomisation was apparently successful as the NIHSS score was 14 in the treatment group and 15 in the placebo group. Five years after the initial publication of this trial further information revealed that in fact patients treated with rt-PA from 91 to 180 minutes after stroke onset had less severe stroke. For example while 19% of patients in the treatment arm had baseline NIHSS of under 5, only 4.2% of cases given placebo were in this category; and among patients with clinically severe stroke (score >20) only 18.3% were given rt-PA while 27.5% were given placebo. Individuals with a higher NIHSS have a low probability of excellent outcome [2]. Randomisation was flawed in this study - the NINDS investigators may have tested two populations with different clinical courses. This introduced bias which may alone have accounted for the efficacy of this drug.

References

1. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute stroke. *N Engl J Med* 1995; **333**:1581-7.
2. Adams HP Jr, Davis PH, Leira EC, et al. Baseline NIH Stroke Scale score strongly predicts outcome after stroke: a report of Trial of Org 10172 in Acute Stroke Treatment (TOAST). *Neurology* 1999; **53**: 126-131.